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Novel regulators of $CD8^+$ T-cell functions in the skin

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Cancer Council statistics show that Australia has the highest rate of skin cancer in the world (twice that of the USA and UK), and predicts 2 in 3 Australians will be diagnosed with skin cancer before the age of 70. Tumour-specific $CD8^+$ T-cells are well-recognised for their importance in eliciting tumour-rejection, however, in many cases tumour-specific $CD8^+$ T-cells within the tumour microenvironment are dysfunctional. The regulation of $CD8^+$ T-cell activity in the tumour microenvironment is poorly understood. This study aimed to explore the mechanisms involved in the regulation of $CD8^+$ T-cells in the skin as a prelude to tumour studies. We have generated a new experimental mouse model in which activated $CD8\beta^+$ T-cells from donor mice were introduced into RAG1KO mice in order to assess $CD8^+$ T-cell deregulation in the absence of conventional-regulatory T-cells (Treg). When RAG1KO mice subsequently received CD4-depleting antibody, $CD8^+$ T-cell-mediated destruction of the ear skin occurred. However, this did not occur in mice administered control-antibody. Analysis of lymph nodes 30 days post $CD8\beta^+$ T-cell transfer showed no evidence of classical $CD4^+FoxP3^+$ Treg indicating regulation is mediated by a separate, distinct cell type. Using the model, we have identified $CD4^+$ cells, which are distinct from classical-Treg, and we are subsequently defining the mechanism by which these cells exert control of $CD8^+$ T-cell function in the skin. Uncovering novel pathways of $CD8^+$ T-cell regulation will shed new light onto regulatory influences of $CD8^+$ T-cell function within tumours and yield opportunities to develop better treatment options for cancer patients.